chemical is a virus attenuating solvent.

4. A method according to claim 3, wherein said solvent is N-tributylphosphate.

5. A method according to claim 3, wherein the virus attenuating solvent is utilized in conjunction with a detergent.

6. A method according to claim 1, wherein the lipid soluble process chemical is a phorbol ester.

7. A method according to claim 1, wherein the phorbol ester is a diterpene ester.

8. A method according to claim 1, wherein the synthetic compound is a synthetic triglyceride and is selected from the group consisting of tristearin, tripalmitin, triolein, trimyristin and combinations thereof.

9. A method according to claim 1, wherein the biological material is selected from the group consisting of blood plasma, blood serum, Fraction I, Fraction II, Fraction III, Fraction IV-1, Fraction IV-4, Fraction V, Fraction VI, fibronectin, antihemophilic factor, prealbumin, retinol-binding protein, albumin, alpha-globulins, beta-globulins, gamma globulins, antithrombin III, prothrombin, plasminogen, fibrinogen, factor XIII, immunoglubin G, immunoglubin A, immunoglubin M, immunoglubin D and immunoglubin E, plasmin inhibitor, prothrombin, thrombin, antithrombin, factor V, factor VII, factor VIII, factor IX and factor X.

10. A method according to claim 1, wherein the oil is contained in an amount of 5 to 50 weight %, based on the weight of the biological fluid.

11. A method of removing lymphokine inducing phorbol esters from lymphokine-containing biological materials selected from the group consisting of mammalian blood, platelet concentrates, white cell concentrates, concentrates of granulocytes, concentrates of monocytes, suspension of cells capable of producing interferon, suspension of cells capable of producing tissue necrosis factor, suspension of cells capable of producing other immune modulators and lymphokines, media separated from said concentrates and suspensions, exudate from cancer cells, exudate from normal cells grown in culture, hydridomas, products from gene splicing, plant cell concentrates, plant cell suspensions, extract of animal tissues, extracts of plant tissues and microorganisms, comprising bringing said biological materials containing said phorbol esters into contact with an effective amount of a naturally occurring oil extracted from a plant or an animal or a synthetic compound of similar chemical structure so as to remove 80% or more of the phorbol esters, the oil being nonflammable, non explosive, compatible with parenterally administered biologics and blood derivatives and pharmaceutically and physiologically tolerable by a human, agitating the resultant mixture, separating out an upper-phase and a lower-phase by sedimentation or centrifugation and decanting the upper-phase.

12. A method according to claim 11, wherein said oil is selected from the group consisting of soybean oil, safflower oil, ricin oil, cottonseed oil, corn oil, peanut oil, olive oil, whale oil and cod liver oil.

13. A method according to claim 11, wherein the phorbol ester is a diterpene ester.

14. A method according to claim 11, wherein the synthetic compound is a synthetic triglyceride and is selected from the group consisting of tristearin, tripalmitin, triolein, trimyristin and combinations thereof.

... Ausab), when corrected for dilution and decantation volume losses, was unchanged.

Example 8

Extraction Of *TNBP* From Intravenous *Immune* *Serum*. *Globulin* (IVISG)

IVISG Sandoz, Hanover, N.J., USA, ("SANDOGLUBULIN") is reconstituted with 4/5 volume distilled water. *TNBP* is added (1:100 w/w) and is finely dispersed by shaking for six hours...

FULL TEXT: 518 lines

ABSTRACT

Antibodies, including monoclonal antibodies (Mabs), can be made substantially free of infectious viruses by storing them in a liquid state at conditions of pH, temperature and time sufficient to inactive substantially all infectious viruses. Preferred inactivation methods involve use of a pH equal to or less than about 4.0 at a temperature of at least about 5 degree(s) C. for at least about 16 hours.

We claim:

1. A method of inactivating viruses in a solution of one or more monoclonal antibodies comprising the step of subjecting the solution to a pH of about 4.0 at a temperature of at least about 5 degree(s) C. for at least about 16 hours to inactivate the viruses.
2. The method of claim 1 wherein in the antibodies are selected from the group consisting of anti-Pseudomonas aeruginosa monoclonal antibodies, anti-factor VIII monoclonal antibodies and anti-TNF monoclonal antibodies.

3. The method of claim 1 wherein the virus inactivated is selected from EBV, Visna, xenotropic and murine ecotropic viruses.

4. The method of claim 1 wherein the virus is a retrovirus.

4/7/97 (Item 4 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

01897105
Utility
PREPARATION OF RETROVIRUS-FREE IMMUNOGLOBULINS
[STORING IN LIQUID STATE AT CONDITIONS OF PH, TEMPERATURE AND TIME TO INACTIVATE ALL INFECTIOUS RETROVIRUSES]

PATENT NO.: 4,948,877
ISSUED: August 14, 1990 (19900814)
INVENTOR(s): Mitra, Gautam, Kensington, CA (California), US (United States of America)
Mozen, Milton M., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Miles Laboratories, Inc , (A U.S. Company or Corporation), Elkhart, IN (Indiana), US (United States of America)
[Assignee Code(s): 55496]
APPL. NO.: 7-192,044
FILED: May 09, 1988 (19880509)
DISCLAIMER: August 09, 2005 (20050809)

This application is a continuation of application Ser. No. 849,612, filed Apr. 8, 1986, now U.S. Pat No. 4,762,714.

FULL TEXT: 425 lines

ABSTRACT

Immune serum globulins (ISG) can be made substantially free of infectious retroviruses by storing the ISG in a liquid state at conditions of pH, temperature and time sufficient to inactivate substantially all infectious retroviruses. Preferred inactivation methods involve use of either of two specified storage conditions: (1) at a pH equal to or less than about 4.25 at a temperature of about 27 degree(s) C. for at least 3 days, or (2) at a pH equal to or less than about 6.8 at a temperature of about 45 degree(s) C. for at least about 8 hours.

We claim:

1. A method of substantially eliminating infectious retroviruses in a final container liquid preparation of immunoglobulin comprising storing said immunoglobulin at a pH equal to or less than about 4.25 at a temperature of about 27 degree(s) C. for at least about 3 days.

2. A method of substantially eliminating infectious retroviruses in a final container liquid preparation of immunoglobulin comprising storing said immunoglobulin at a pH equal to or less than about 6.8 at a temperature of about 45 degree(s) C. for at least about 8 hours.

3. The method of claim 1 or 2 wherein the retrovirus is the LAV strain associated with Acquired Immune Deficiency Syndrome.

4. The method of claim 1 or 2 wherein the immunoglobulin comprises purified antibodies in liquid form suitable for intravenous adminstration.

viral inactivation as was precipitation of fraction II from filtrate III with 25% ethanol. Liquid immunoglobulin preparations spiked with LAV and incubated at 27 degree(s) C. for 3 days resulted in an additional 1,000-10,000-fold reduction of LAV titer. Our results support the clinical and epidemiological evidence that therapeutic immunoglobulin preparations prepared by Cohn-Oncley cold ethanol processing (at least about 18% v/v alcohol, pH<=5.4) and then stored at a pH equal to or less than about 5.4 and a temperature of at least 27 degree(s) C. for at least 3 days, do not transmit retroviruses such as the LAV strain of the AIDS virus. Similar fractionation followed by storage at a higher pH (6.8) followed by a storage at a higher temperature (45 degree(s) C.) for at least 8 hours also appears effective in avoiding transmission of the retroviruses.

We claim:

1. A method of inactivating hepatitis C viruses in an aqueous solution of a human immunoglobulin product comprising the step of incubating the solution at a pH of about 3.5 to about 5.0 at a temperature of about 21 degree(s) C. for at least about 21 days to inactivate substantially all the hepatitis C virus.

2. The method of claim 1 wherein the solution is suitable for intravenous administration to a human.

3. The method of claim 1 wherein the incubation is at a pH of about 4.24.

4. The method of claim 1 wherein the method results in the inactivation of at least 10 sup 3 infectious doses of HCV per ml of solution.

4/7/96 (Item 3 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02126795

Utility
PREPARATION OF VIRUS-FREE ANTIBODIES
[Subjecting solution to pH of about 4 a temperature of at least 5 degrees delsius for at least 16 hours]

PATENT NO.: 5,159,064
ISSUED: October 27, 1992 (19921027)
INVENTOR(s): Mitra, Gautam, Kensington, CA (California), US (United States of America)
Mozen, Milton M., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Miles Inc , (A U.S. Company or Corporation), Elkhart, IN (Indiana), US (United States of America)
[Assignee Code(s): 55496]
APPL. NO.: 7-471,571
FILED: January 29, 1990 (19900129)
DISCLAIMER: August 09, 2005 (20050809)

This is a continuation-in-part of Ser. No. 07-192,044 filed on May 9, 1988, U.S. Pat. No. 4,948,877, which is a continuation of patent application Ser. No. 06-849,612 filed Apr. 4, 1986, now U.S. Pat. No. 4,762,714.

having a protein content of about 25-30% and Fraction II paste which comprises the steps:
a. suspending said paste in water to form a solution of low ionic strength having a conductance of about 300 times 10 sup -6 cm sup -6 ohm sup -1 at a pH of about 4.8 to 6.5 to produce a precipitate and filtrate,
b. fractionally precipitating impurities from said filtrate by adding polyethylene glycol to 4% weight/volume and then 5% weight/volume,
c. precipitating the gamma globulin by adding polyethylene glycol to 12% weight/volume at a pH of about 8 slashed zero

said process being carried out at a temperature of about 0 degree(s) to 20 degree(s) C.

2. A process according to claim 1 wherein the pH at which the paste is extracted is about 5.7 to 5.9.

3. A process according to claim 2 wherein 1 kg. of Fraction II + III paste is extracted at pH 5.8 with about 30 liters of pyrogen-free water.

4. A process according to claim 1 wherein the polyethylene glycol has a molecular weight of about 4,000 to 6,000.

5. A process according to claim 4 wherein the polyethylene glycol has a molecular weight of about 4,000.

6. A process according to claim 5 wherein the process is carried out at a temperature of about 0 degree(s) to 5 degree(s) C.

4/7/93 (Item 1 from file: 653)
DIALOG(R)File 653:US Pat.Fulltext

01696534
Utility
PREPARATION OF RETROVIRUS-FREE IMMUNOGLOBULINS
[COLD ETHANOL AND STORAGE]

PATENT NO.: 4,762,714 ?
ISSUED: August 09, 1988 (19880809)
INVENTOR(s): Mitra, Gautam, Kensington, CA (California), US (United States of America)
Mozen, Milton M., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Miles Laboratories, Inc , (A U.S. Company or Corporation), Elkhart, IN (Indiana), US (United States of America)
[Assignee Code(s): 55496]
APPL. NO.: 6-849,612
FILED: April 08, 1986 (19860408)
FULL TEXT: 417 lines

ABSTRACT

Immune serum globulins (ISG) can be made substantially free of infectious retroviruses by preparing the ISG from human plasma using a cold ethanol plasma fractionation process at a pH equal to or less than 5.4 and then storing the ISG at either of two specified storage conditions: (1) at a pH equal to or less than about 4.25 at a temperature of about 27 degree(s) C.

for at least 3 days, or (2) at a pH equal to or less than about 6.8 at a temperature of about 45 degree(s) C. for at least about 8 hours. pg,10

We claim:

1. A method of preparing an immune serum globulin substantially free of infectious retroviruses comprising the steps of
(1) preparing an immune serum globulin from a human plasma source using a cold ethanol process at a pH equal to or less than about 5.4 and then
(2) storing the globulin at a pH equal to or less than about 4.25 at a temperature of about 27 degree(s) C. for at least about 3 days.

2. A method of preparing an immune serum globulin substantially free of infectious retroviruses comprising the steps of
(1) preparing an immune serum globulin from a human plasma source using a cold ethanol process at a pH equal to or less than about 5.4 and then
(2) storing the globulin at a pH equal to or less than about 6.8 at a temperature of about 45 degree(s) C. for at least about 8 hours.

4/7/94 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02418426
Utility
PREPARATION OF HUMAN IMMUNOGLOBULIN FREE OF HEPATITIS C

PATENT NO.: 5,419,906
ISSUED: May 30, 1995 (19950530)
INVENTOR(s): Mitra, Gautam, Kensington, CA (California), US (United States of America)
Mozen, Milton M., Berkeley, CA (California), US (United States of America)
Louie, Robert E., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Miles Inc, (A U.S. Company or Corporation), Elkhart, IN (Indiana), US (United States of America)
[Assignee Code(s): 55496]
APPL. NO.: 7-965,658
FILED: October 23, 1992 (19921023)

This is a Continuation-in-part of Ser. No. 07-471,571, filed Jan. 29, 1990, now U.S. Pat. No. 5,159,064, which is a Continuation-in-part of Ser. No. 07-192,044 filed May 9, 1988, now U.S. Pat. No. 4,948,877, which is a Continuation of patent application Ser. No. 06-849,612 filed Apr. 4, 1986 now U.S. Pat. No. 5,762,714.

FULL TEXT: 476 lines

ABSTRACT

The effects of Cohn-Oncley cold alcohol fractionation on infectivity of two prototype retroviruses, mouse xenotropic type C and the LAV strain of AIDS retrovirus result in a significant reduction in retrovirus titer. At least a 100,000-fold reduction of LAV was obtained when fractionating plasma to fraction II. Adjustment to pH 4.0 at filtrate III was as effective for

comprises the steps:
a. suspending said paste in water to form a solution of low ionic strength having a conductance of about 300-10 sup -6 cm sup -1 ohm sup -1 at a pH of about 4.8 to 6.5 to produce a precipitate and a filtrate,
b. fractionally precipitating impurities from said filtrate by adding polyethylene glycol to 4% weight/volume and then 5% weight/volume,
c. precipitating the gamma globulin by adding polyethylene glycol to 12% weight/volume at a pH of about 8 slashed zero

2. A solution of the gamma globulin according to claim 1 for intravenous administration comprising the gamma globulin in a aqueous solution containing albumin, a non-ionic surfactant, glycine and acetic acid-acetate buffer at pH 5.4-6.7.

3. A solution of gamma globulin according to claim 2 wherein the non-ionic surfactant is Tween 80 or Pluronic 68.

4/7/92 (Item 3 from file: 652)
DIALOG(R)File 652:US Patents Fulltext

00973471
Utility
METHOD OF PRODUCING INTRAVENOUSLY INJECTABLE GAMMA GLOBULIN AND A GAMMA GLOBULIN SUITABLE FOR CARRYING OUT THE METHOD
[FRACTIONALLY PRECIPITATING IMPURITIES BY ADDING POLYOXYETHYLENE GLYCOL]

PATENT NO.: 4,093,606
ISSUED: June 06, 1978 (19780606)
INVENTOR(s): Coval, Myer Louis, 6241 Chelton Dr., Oakland, CA (California), US (United States of America) 68000]
APPL. NO.: 5-688,621
FILED: May 21, 1976 (19760521)

REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of my application Ser. No. 550,467 filed Feb. 18, 1975. Now abandoned

FULL TEXT: 313 lines

ABSTRACT

A process is provided for the preparation of a gamma globulin suitable for intravenous administration from the readily available Fraction II or II + III plasma protein paste. The Fraction II or II + III paste is extracted with water at a pH of 4.8 - 6.5 and impurities are fractionally precipitated by addition of polyethylene glycol to 4% of wt./vol. and then 5% wt./vol. The desired gamma globulin is then precipitated at a pH 8.0 by addition of polyethylene glycol to 12% wt./vol.

I claim:

1. A process for preparing a gamma globulin substantially devoid of anticomplementary activity and suitable for intravenous administration, from a material selected from the Fraction II + III plasma protein paste

Multistep purificn. of *immune* *serum* *globulin* fraction from a crude plasma protein fraction involves pptn of non-serum globulin proteins using a protein precipitant, adding a *virus*-inactivating agent and absorbing the globulins onto a cation exchange resin. The eluate is ultrafiltrated to conc. the globulins and separate from low mol.wt. species. the conc is contracted with an anion exchange resin to absorb the contaminants, passed through a resin and the filtrate is washed.

USE/ADVANTAGE - Avoids active viruses and contaminating lipids etc. Efficient and adaptable to large-scale prodn. Dwg.0/0

Derwent Class: B04;
Int Pat Class: A61K-039/39; C07K-003/12; C07K-003/22; C07K-003/26; C07K-003/28; C07K-015/06

4/7/90 (Item 1 from file: 652)
DIALOG(R)File 652:US Patents Fulltext

01050435

Utility

INJECTABLE GAMMA GLOBULIN [DEVOID OF ANTICOMPLEMENTARY ACTIVITY, FRACTIONALLY PRECIPITATED AND PURIFIED WITH POLYOXYETHYLENE GLYCOL]

PATENT NO.: 4,165,370
ISSUED: August 21, 1979 (19790821)
INVENTOR(s): Coval, Myer Louis, 6241 Chelton Dr., Oakland, CA (California), US (United States of America), 94611 68000]
APPL. NO.: 5-900,616
FILED: April 27, 1978 (19780427)

REFERENCE TO RELATED APPLICATION

This is a division of application Ser. No. 688,621, filed May 21, 1976, now U.S. Pat. No. 4,093,606. which in turn is a continuation-in-part of my application Ser. No. 550,467 filed Feb. 18, 1975 now abandoned.

FULL TEXT: 307 lines

ABSTRACT

A process is provided for the preparation of a gamma globulin suitable for intravenous administration from the readily available Fraction II or II + III plasma protein paste. The Fraction II or II + III paste is extracted with water at a pH of 4.8-6.5 and impurities are fractionally precipitated by addition of polyethylene glycol to 4% of wt./vol. and then 5% wt./vol. The desired gamma globulin is then precipitated at a pH 8.0 by addition of polyethylene glycol to 12% wt./vol.

I claim:

1. A gamma globulin suitable for intravenous administration prepared according to the following process:
a process for preparing a gamma globulin substantially devoid of anticomplementary activity and suitable for intravenous administration, from a material selected from the Fraction II+III plasma protein paste having a protein content of about 25--30% and Fraction II paste which

and Applied Microbiology
Use of the organic solvent, tri(n-butyl)phosphate (TNBP), and detergents for the inactivation of viruses in labile blood derivatives was evaluated by addition of marker viruses (VSV, Sindbis, Sendai, EMC) to anti-hemophilic factor (AHF) concentrates. The rate of virus inactivation obtained with TNBP plus Tween 80 was superior to that observed with ethyl ether plus Tween 80, a condition previously shown to inactivate greater than or equal to 106.9 CID50 of hepatitis B and greater than or equal to 104 CID50 of Hutchinson strain non-A, non-B hepatitis. The AHF recovery after TNBP/Tween treatment was greater than or equal to 90 percent. Following the reaction, TNBP could be removed from the protein by gel exclusion chromatography on Sephadex G25; however, because of its large micelle size, Tween 80 could not be removed from protein by this method. Attempts to remove Tween 80 by differential precipitation of protein were only partially successful.

19/7/18 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02416424
Utility
METHOD OF INACTIVATION OF VIRAL AND BACTERIAL BLOOD CONTAMINANTS

PATENT NO.: 5,418,130
ISSUED: May 23, 1995 (19950523)
INVENTOR(s): Platz, Matthew S., Columbus, OH (Ohio), US (United States of America)
Goodrich, Jr. Raymond P., Pasadena, CA (California), US (United States of America)
Yerram, Nagendar, South Pasadena, CA (California), US (United States of America)
ASSIGNEE(s): Cryopharm Corporation, (A U.S. Company or Corporation), Pasadena, CA (California), US (United States of America) [Assignee Code(s):
APPL. NO.: 8-91,674
FILED: July 13, 1993 (19930713)

This is a continuation-in-part of 08-047,749, filed Apr. 14, 1993, which is a continuation in part of Ser. No. 07-825,691, filed Jan. 27, 1992, now abandoned, which is a continuation-in-part of Ser. No. 07-685,931, filed Apr. 16, 1991, now abandoned, which is a continuation-in-part of Ser. No. 07-656,254, filed Feb. 15, 1991, now abandoned, which is a continuation-in-part of Ser. No. 07-632,277, filed Dec. 20, 1990, now abandoned, which is a continuation-in-part of Ser. No. 07-510,234, filed Apr. 16, 1990, now abandoned.

FULL TEXT: 2595 lines

ABSTRACT

A method is provided for inactivating viral and/or bacterial contamination in blood cellular matter, such as erythrocytes and platelets, or protein fractions. The cells or protein fractions are mixed with chemical sensitizers and irradiated with, for example, UV, visible, gamma or X-ray radiation. In particular, quaternary ammonium or phosphonium substituted,

halo-psoralen compounds are described as being useful.

What is claimed is:

1. A process for reducing vital, and/or bacterial contaminants in a composition comprising blood, a blood component, cell cultures or a component of a cell culture, comprising the steps:
mixing said composition in a liquid state with a chemical radiation sensitizer capable of targeting said vital, and/or bacterial contaminants, wherein said sensitizer is a compound of the formula: [See structure in original document] wherein u is an integer from 1 to 6; X is an anionic counterion; R sub 1, R sub 2, R sub 3, R sub 4, R sub 5, and R sub 6 are independently halo; H; linear or branched alkyl of 1-10 carbon atoms; linear or branched alkoxy of 1-10 carbon atoms; (CH sub 2) sub m O(CH sub 2) sub p Z sup sym R', R", R"' or --O(CH sub 2) sub n Z sup sym R', R", R"' wherein n, m and p are independently integers from 1 to 10 and R', R", R"' are independently H or linear or branched alkyl of 1 to 10 carbon atoms; at least one of R sub 1, R sub 2, R sub 3, R sub 4, R sub 5, and R sub 6 is halo; and at least one of R sub 1, R sub 2, R sub 3, R sub 4, R sub 5, and R sub 6 is (CH sub 2) sub m O(CH sub 2) sub p Z sup sym R', R", R"' or --O(CH sub 2) sub n Z sup sym R', R"'; Z is N or P; and
exposing said composition and sensitizer to electromagnetic radiation of sufficient wavelength and intensity for a period of time sufficient to activate said sensitizer whereby the activation of said sensitizer reduces said contamination in said composition.

2. A process according to claim 1 wherein said composition comprises whole blood or a cellular fraction prepared from whole blood.

3. A process according to claim 2 wherein said blood cell fraction comprises red blood cells, platelets, white blood cells, or stem cells.

4. A process according to claim 1 wherein said composition comprises whole plasma or a blood plasma fraction.

5. A process according to claim 4 wherein said blood plasma fraction comprises plasma protein fractions.

6. A process according to claim 5 wherein said plasma protein fractions comprise serum albumin, immune globulins, or a clotting factor.

7. A process according to claim 6 wherein said clotting factor comprises Factor VIII.

8. A process according to claim 1 wherein said cell culture comprises growth media containing serum supplements.

9. A process according to claim 8 wherein said serum supplements comprise whole animal serum or fractions derived from whole animal serum.

10. A process according to claim 9 wherein said animal serum comprises bovine serum.

11. A process according to claim 10 wherein said bovine serum comprises fetal calf serum.

12. A process according to claim 8 wherein said growth media comprises serum supplements used to propagate mammalian cell lines.

13. A process according to claim 12 wherein said culture comprises mammalian cell lines containing recombinant genetic material for expression of recombinant proteins.

14. A process according to claim 13 wherein said culture comprises recombinant plasma proteins.

15. A process according to claim 14 wherein said recombinant plasma proteins comprise recombinant serum albumin or recombinant clotting factors.

16. A process according to claim 15 wherein said recombinant clotting factors comprise recombinant Factor VIII.

17. A process according to claim 12 wherein said mammalian cell lines comprise hybridoma cell lines.

18. A process according to claim 17 wherein said hybridoma cell lines produce monoclonal antibodies.

19. A process according to claim 1 wherein said composition comprises pharmaceutically useful proteins.

20. A process according to claim 19 wherein said proteins comprise growth factors and hormones.

21. A process according to claim 1 wherein said electromagnetic radiation comprises ultraviolet light.

22. A process according to claim 21 wherein said ultraviolet light is characterized by wavelengths of 400 nanometers or less.

23. A process according to claim 1 wherein R sub 4 is --O--CH sub 2 -- sub n N sup sym R'R"R"'.

24. A process according to claim 23 wherein R', R" and R"' are ethyl.

25. A process according to claim 24 wherein R sup 6, R sup 5, R sup 2 and R sup 1 are hydrogen

26. A process according to claim 25 wherein R sup 3 is H or halo.

27. A process according to claim 26 wherein R sup 3 is bromo.

28. A process according to claim 27 wherein n=3.

29. A process according to claim 23 wherein R', R" and R"' are methyl.

30. A process according to claim 29 wherein R sup 1, R sup 2, R sup 5 and R sup 6 are hydrogen and R sup 3 is halo.

31. A process according to claim 30 wherein R sup 3 is bromo.

32. A process according to claim 31 wherein n=3, 4, 5, 6 or 7.

33. A process according to claim 27 wherein n=2.

34. A process according to claim 23 wherein R', R" and R"' are n-propyl.

35. A process according to claim 34 wherein R sup 1, R sup 2, R sup 5 and

R sup 6 are hydrogen and R sup 3 is halo.

36. A process according to claim 35 wherein R sup 3 is bromo.

37. A process according to claim 1 wherein R sub 4 is --O--CH' sub 2 -- sub n P sup + R'R"R"'.

38. A process according to claim 37 wherein R', R" and R"' are methyl, ethyl, n-propyl or n-butyl.

39. A process according to claim 38 wherein R sup 1, R sup 2, R sup 5 and R sup 6 are hydrogen and R sup 3 is halo.

40. A process according to claim 39 wherein R sup 3 is bromo.

41. A process according to claim 1 wherein said sensitizer is a compound of the formula: [See structure in original document]

b. alkylating all of the thus-produced --SH groups of the thus-reduced ISG by reaction with a molar equivalent excess of an alkylating agent;
c. separating the thus-produced modified ISG from the other reaction products and any residual reactants to produce a solution of substantially pure modified ISG; and
d. sterilizing the solution of the substantially pure modified ISG to render it intravenously injectable

15. A lyophilized modified immune serum globulin according to claim 13 wherein the alkylated mercapto groups are --S--CH sub 2 CONH sub 2 groups.

16. In the art of immune serum globulin administration in human therapy, the improvement which comprises administering intravenously a composition according to claim 1.

17. In the art of immune serum globulin administration in human therapy, the improvement which comprises administering intravenously a composition according to claim 5.

18. In the art of immune serum globulin administration in human therapy, the improvement which comprises administering intravenously a composition according to claim 6.

19. In the art of immune serum globulin administration in human therapy, the improvement which comprises administering intravenously a composition according to claim 8.

20. In the art of immune serum globulin administration in human therapy, the improvement which comrpises administering intravenously a composition according to claim 11.

7/7/17 (Item 1 from file: 654)
DIALOG(R)File 654:US PAT.FULL.

02146655
Utility
PROCESS FOR PURIFYING IMMUNE SERUM GLOBULINS

PATENT NO.: 5,177,194
ISSUED: January 05, 1993 (19930105)
INVENTOR(s): Sarno, Maria E., Cerritos, CA (California), US (United States of America)
Graf, Clifford, Lake View Terrace, CA (California), US (United States of America)
Neslund, Gerald, Diamond Bar, CA (California), US (United States of America)
Yung, Sau-Gee, Rialto, CA (California), US (United States of America)
Burnham, James, Laverne, CA (California), US (United States of America)
Kim, Jean, La Canada, CA (California), US (United States of America)
Vasquez, Rodolfo A., Norwalk, CA (California), US (United States of America)
ASSIGNEE(s): Baxter International, Inc , (A U.S. Company or Corporation), Deerfield, IL (Illinois), US (United States of America)

(> 1500 ng/pup), all preparations protected well. At marginal doses (750 ng/pup), rats given reduced and alkylated globulin had a significantly greater incidence of bacteremia ($P < 0.05$), meningitis ($P < 0.01$) and death ($P < 0.05$) and a higher magnitude of bacteremia ($P < 0.02$) than rats who received pH4-treated or ultrafiltered globulins. These differences were not due to differences in anticapsular antibody concentrations achieved in the serum. The 50% protective serum concentrations of anticapsular antibody in this model were 200-300 ng/ml for reduced and alkylated globulin and 100-200 ng/ml for acid-treated globulin. Absorption of the globulins with purified H. influenzae b capsule reduced in vitro bactericidal activity and rat protective activity. However, the magnitude of bacteremia was lower in rats receiving adsorbed pH 4-treated globulin than in those receiving absorbed reduced and alkylated globulin ($P < 0.05$). Thus, reduced and alkylated IgG provides significantly less protective activity against H. influenzae b infection with this model than globulins not so modified, and the altered Fe function of the IgG, such as the decreased ability to fix complement by the classical pathway or decreased Fc-mediated opsonization, may be responsible for this impairment.

7/7/16 (Item 2 from file: 652)
DIALOG(R)File 652:US Patents Fulltext

00777920

Utility
PHARMACEUTICAL COMPOSITIONS COMPRISING INTRAVENOUSLY INJECTABLE MODIFIED SERUM GLOBULIN, ITS PRODUCTION AND USE

PATENT NO.: 3,903,262
ISSUED: September 02, 1975 (19750902)
INVENTOR(s): Pappenhagen, Albert R., Moraga, CA (California), US (United States of America)
Lundblad, John L., El Cerrito, CA (California), US (United States of America)
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[Assignee Code(s): 21768]
APPL. NO.: 5-473,209
FILED: May 24, 1974 (19740524)

This is a continuation-in-part of Application Ser. No. 234,006, filed Mar. 13, 1972, now abandoned.

FULL TEXT: 1277 lines

ABSTRACT

A pharmaceutical composition comprising, in a pharmaceutically acceptable aqueous carrier adapted for intravenous administration, an intravenously injectable, substantially pure modified immune serum globulin consisting essentially of intact immune serum globulin chains having intact intrachain disulfide linkages and cleaved at at least one interchain disulfide linkage, each cleaved disulfide linkage being replaced by a pair of alkylated mercapto groups, the cleaved chains remaining united by non-covalent association so that the apparent molecular weight of the

modified serum globulin in non-dissociating solvents is substantially the same as unmodified *immune* serum globulin, said modified *immune* serum globulin being substantially free from both actual and latent anti-*complement* activity and having substantially the biological half-life and spectrum of antibody activity of corresponding unmodified *immune* *serum* *globulin* , said modified immune serum globulin having an H sub 2 L sub 2 content of less than 7 percent, an H sub 2 L sub 2 + H sub 2 L + H sub 2 content of 5-30 percent and an HL + H + L content of 95-70 percent wherein H is an intact heavy chain and L an intact light chain, and having an S-alkylated cysteine content of about 5.6-9.5 moles per mole of immune serum globulin; said modified immune serum globulin being produced by selectively reducing a mildly alkaline aqueous solution of an immune serum globulin with dithiothreitol or dithioerythritol, alkylating the thus-reduced interchain disulfide groups, and separating the thus-modified globulin from the non-proteinaceous reaction products.

What is claimed is:

1. A pharmaceutical composition comprising a sterile solution, in a pharmaceutically acceptable aqueous carrier adapted for intravenous administration, of an intravenously injectable, substantially pure modified immune serum globulin consisting essentially of intact immune serum globulin chains having intact intrachain disulfide linkages and cleaved at at least one interchain disulfide linkage, each cleaved idsulfide linkage being replaced by a pair of alkylated mercapto groups produced by a process which comprises the steps of

a. selectively reducing to --SH groups at least one interchain disulfide linkage of immune serum globulin with a reducing agent under conditions which leave the intrachain disulfide linkages and the remainder of the molecule substantially intact; and

b. alkylating all of the thus-produced --SH groups of the thus-reduced ISG by reaction with a molar equivalent excess of an alkylating agent,

the cleaved chains remaining united by non-covalent association so that the apparent molecular weight of the modified serum globulin in non-dissociating solvents is substantially the same as unmodified immune serum globulin, said modified immune serum globulin being, in accordance with said process, thereby rendered substantially free from both actual and latent anticomplement activity and having substantially the biological half-life and spectrum of antibody activity of corresponding unmodified immune serum globulin, said modified immune serum globulin having an H sub 2 L sub 2 content of less than 7 percent, an H sub 2 L sub 2 + H sub 2 L + H sub 2 content of 5-30 percent and an HL + H + L content of 95-70 percent wherein H is an intact heavy chain and L an intact light chain, and having an S-alkylated cysteine content of 5.6 - 9.5 moles per mole immune serum globulin.

2. A composition according to claim 1 wherein the alkylated mercapto groups are --S--CH sub 2 --CONH sub 2 groups.

3. A composition according to claim 1 wherein the said modified immune serum globulin has an average of about 5.6-8.5 S-alkylated cysteine groups per molecule.

4. A composition according to claim 3 wherein the alkylated mercapto groups are --S--CH sub 2 --CONH sub 2 groups.

5. A composition according to claim 1 wherein the modified serum globulin

is hyperimmune.

6. A composition according to claim 5 wherein said modified hyperimmune serum globulin is tetanus immune globulin.

7. A composition according to claim 6 wherein the alkylated mercapto groups are --S--CH sub 2 CONH sub 2 groups.

8. A composition according to claim 5 wherein said modified hyperimmune serum globulin is rabies immune globulin.

9. A composition according to claim 8 wherein the alkylated mercapto groups are --S--CH sub 2 CONH sub 2 groups.

10. A composition according to claim 1 as an about 10 percent solution of the modified immune serum globulin.

11. A composition according to claim 1 wherein the modified serum globulin is hepatitis immune globulin.

12. A composition according to claim 1 as an about 5 percent solution of the modified immune serum globulin.

13. Lylophilized, sterile, substantially pure, and when reconstituted as a 5-10 percent solution, intravenously injectable, modified serum globulin consisting essentially of intact immune serum globulin chains having intact intrachain disulfide linkages and cleaved at at least one interchain disulfide linkage, each cleaved disulfide linkage being replaced by a pair of alkylated mercapto groups produced by a process which comprises the steps of

a. selectively reducing to --SH groups at least one interchain disulfide linkage of immune serum globulin with a reducing agent under conditions which leave the intrachain disulfide linkages and the remainder of the molecule substantially intact; and

b. alkylating all of the thus-produced --SH groups of the thus-reduced ISG by reaction with a molar equivalent excess of an alkylating agent,

the cleaved chains remaining united by non-covalent association so that the apparent molecular weight of the modified serum globulin in non-dissociating solvents is substantially the same as unmodified immune serum globulin, said modified immune serum globulin being, in accordance with said process, thereby rendered substantially free from both actual and latent anticomplement activity and having substantially the biological half-life and spectrum of antibody activity of corresponding unmodified immune serum globulin, said modified immune serum globulin having an H sub 2 L sub 2 content of less than 7 percent, an H sub 2 L sub 2 + H sub 2 L + H sub 2 content of 5-30 percent and an HL + H + L content of 95-70 percent wherein H is an intact heavy chain and L an intact light chain, ahd having an S-alkylated cysteine content of 5.6 - 9.5 moles per mole immune sercum globulin.

14. A method for rendering immune serum globulin substantially free from both actual and latent anticomplement activity while retaining substantially the biological half-life and spectrum of antibody activity which comprises the steps of

a. reducing to --SH groups at a pH of about 7.2 - 9 from about 2.8 to 4.75 of the disulfide linkages of 1-18 percent solution of the ISG with dithioerythritol or diithiothreitol under conditions of time, temperature and ratio of reducing agent to ISG shown in FIG. 4 of the drawings; pg,55

4/7/77 (Item 10 from file: 434)
DIALOG(R)File 434:SciSearch(R)

10617193 Genuine Article#: ET595 Number of References: 27
Title: A SERAL EPIDEMIOLOGIC-STUDY OF HIV TRANSMITTED THROUGH HUMAN SERAL GAMMA-GLOBULIN PREPARATIONS
Author(s): LI J; JIANG DH; WANG LF; ZENG Y; LI D; LI GX; LIU YY; SHAO YM; ZHU ZH; KONG J; FENG XX; JING SN; WANG J; LIU JX
Corporate Source: JINING HYG & ANTIEPIDEM STN,27 GONG QINGTUAN RD/JINIG CITY 272145//PEOPLES R CHINA/; CHINESE ACAD PREVENT MED/BEIJING//PEOPLES R CHINA/; TV UNIV SHENGLI OIL FIELD/SHENGLI//PEOPLES R CHINA/; JINING HOSP/SHANDONG//PEOPLES R CHINA/; JINING MED COLL/JINING//PEOPLES R CHINA/; HOSP JINING CITY,RD TRANSPORTAT CO/JINING//PEOPLES R CHINA/; JINING HYG BUR/SHANDONG//PEOPLES R CHINA/; YANZHOU CTY HOSP/SHANDONG//PEOPLES R CHINA/
Journal: INTERNATIONAL JOURNAL OF EPIDEMIOLOGY, 1990, V19, N4, P1057-1060
Language: ENGLISH Document Type: ARTICLE

4/7/82 (Item 3 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

432333 80021500406
Transmission of hepatitis B by immune serum globulin.;
Tabor,E. ; Gerety,R.J.
(Hepatitis Branch, Div. Blood and Blood Prod., Bur. Biol., FDA, Bethesda, MD 20205, USA)
Lancet ; 2(8155), 1293 1979 ;
Language: English
Document Type: Journal article-letter
Subfile: 22 Virology Abstracts;
Tests were performed on a sample of immune serum globulin (ISG) from a batch implicated in an outbreak of hepatitis B. Although the ISG was hepatitis B virus negative by counter-electrophoresis, HBsAg was detected by radioimmunoassay and by reverse passive haemagglutination. A chimpanzee given 10 ml of the ISG developed hepatitis B. The transmission of hepatitis by blood products is a problem which is likely to decline as more sensitive tests for the detection of HBsAg come into common use.
?t s4/7/82,89,90,92,93,94,96,97

4/7/16 (Item 12 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

5697780 BIOSIS Number: 33092801
HDV INFECTION FROM BLOOD AND BLOOD PRODUCTS
SARACCO G; PONZETTO A; FORAZNI B; HELE C; ROSINA F; LOSTIA O; CAIOLA S; RIZZETTO M
DIV. GASTROENTEROLOGIA, OSPEDALE MOLINETTE, TORINO, ITALY.
RIZZETTO, M., J. L. GERIN AND R. H. PURCELL (ED.). PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH, VOL. 234. THE HEPATITIS DELTA VIRUS AND ITS INFECTION; INTERNATIONAL SYMPOSIUM, SAINT VINCENT, ITALY, JUNE 19-20, 1986. XXXVIII+551P. ALAN R. LISS, INC.: NEW YORK, NEW YORK, USA. ILLUS. ISBN 0-8451-5084-7. 0 (0). 1987. 361-366. CODEN: PCBRD
Language: ENGLISH

7/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

4865363 BIOSIS Number: 79107678
INTRAVENOUS AND STANDARD *IMMUNE* *SERUM* *GLOBULIN* PREPARATIONS INTERFERE WITH UPTAKE OF IODINE-125-LABELED *COMPLEMENT* C-3 ONTO SENSITIZED ERYTHROCYTES AND INHIBIT HEMOLYTIC *COMPLEMENT* ACTIVITY
BERGER M; ROSENKRANZ P; BROWN C Y
DEPARTMENT OF PEDIATRICS, CASE WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE, RAINBOW BABIES AND CHILDRENS HOSPITAL, 2101 ADELBERT ROAD, CLEVELAND, OHIO 44106.
CLIN IMMUNOL IMMUNOPATHOL 34 (2). 1985. 227-236. CODEN: CLIIA
Full Journal Title: Clinical Immunology and Immunopathology
Language: ENGLISH
Antibody-sensitized sheep erythrocytes were used as a model to determine the effects of therapeutic *immune* *serum* *globulin* (ISG) preparations on the ability of this particulate activator to fix [*complement*] C3 and initiate hemolysis. Both standard and i.v. forms of ISG inhibit uptake of 125I-C3, presumably by competing for the deposition of nascent C3b molecules onto the erythrocytes. Both forms of ISG also inhibit hemolytic activity of whole serum or purified complement components. The inhibition appears to be a specific property of IgG itself, since similar inhibition was not caused by equivalent concentrations of human serum albumin, and was not affected by the buffer in which the ISG was dissolved. Interference with C3 uptake onto antibody-sensitized platelets and/or inhibition of hemolytic complement activity could contribute to the efficacy of high dose i.v. ISG in idiopathic thrombocytopenic purpura.

7/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

4834888 BIOSIS Number: 79077203
DECREASED PROTECTIVE EFFICACY OF REDUCED AND ALKYLATED HUMAN IMMUNE SERUM GLOBULIN IN EXPERIMENTAL INFECTION WITH HAEMOPHILUS-INFLUENZAE TYPE B
SCHREIBER J R; BARRUS V A; SIBER G R
DEPARTMENT INFECTIOUS DISEASE, DANA-FARBER CANCER INSTITUTE, BOSTON, MASSACHUSETTS 02115.
INFECT IMMUN 47 (1). 1985. 142-148. CODEN: INFIB
Full Journal Title: Infection and Immunity
Language: ENGLISH
Conventionally prepared immune serum globulin frequently produces severe side effects when administered i.v. A modified preparation in which 4-5 interchain disulfide bonds have been reduced and alkylated has been made for i.v. use. However, reduction and alkylation may affect Fc-mediated functions of IgG, particularly its ability to fix *complement* by the classical pathway. To determine whether reduction and alkylation alters the protective activity of *immune* *serum* *globulin* in vivo, it was compared with 2 less harshly prepared globulins (pH 4 treated or ultrafiltered) in an infant rat model of H. influenzae b infection. Antibody binding to the capsular and noncapsular components of H. influenzae b and in vitro bactericidal activity were similar in the globulin preparations. Infant rats were treated with various doses of globulins adjusted to provide identical concentrations of anticapsular antibodies as measured by the Farr radioactive antigen binding assay. At high doses of anticapsular antibody

19/7/3 (Item 2 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

11346834 BIOSIS Number: 97546834
Virus-inactivated plasma
Koehler M; Wieding J U
Abt. Transfusionsmed., Klin. Univ. Goettingen, Robert-Koch-Str. 40, D-37075 Goettingen, GER
Infusionstherapie und Transfusionmedizin 21 (SUPPL. 1). 1994. 73-76.
Full Journal Title: Infusionstherapie und Transfusionmedizin
ISSN: 1019-8466
Language: GERMAN
Print Number: Biological Abstracts Vol. 098 Iss. 012 Ref. 164457

Two different virus inactivated plasma preparations are available in Germany. Methylen bluephotoxidized (MB) plasma is plasma from a single donation, which is photoxidized using 1 mu-M methylene blue and visible light (1 hour 60,000 Lux). Photochemical inactivation reduces HIV by at least 5 log-10, but also fibrinogen is altered. To date, the clinical significance of this finding is still unclear, since prospective clinical studies are lacking. Solvent detergent (SD) plasma is manufactured from a pool of about 2000 *plasma* donations, and triton-X-100 and tri-n-butylphosphate (*TNBP*) are added for *virus* inactivation. HIV and hepatitis viruses are thus reduced by 5 to 6 log-10. SD treatment reduces protein S and alpha-2-antiplasmin by about 40%. Clinical studies have already demonstrated, that SD plasma is comparable with untreated, native fresh frozen plasma in terms of efficacy.

19/7/4 (Item 3 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

10058444 BIOSIS Number: 95058444
VIRUS INACTIVATION OF FRESH FROZEN PLASMA BY A SOLVENT DETERGENT PROCEDURE BIOLOGICAL RESULTS
PIQUET Y; JANVIER G; SELOSSE P; DOUTREMEPUICH C; JOUNEAU J; NICOLLE G; PLATEL D; VEZON G
CENTRE REGIONAL DE TRANSFUSION SANGUINE, PLACE AMELIE-RABA-LEON, BP 24, F-33035 BORDERAUX CEDEX, FRANCE.
VOX SANG 63 (4). 1992. 251-256. CODEN: VOSAA
Full Journal Title: Vox Sanguinis
Language: ENGLISH

In order to increase the safety of blood products, we have developed a procedure for the virus inactivation of fresh frozen plasma. Several batches have been prepared and with the first 10 batches, each of them composed of 60 litres of *plasma*, we have determined a set of biological parameters. *Virus* inactivation was realised using *TnBP* (1%) and Octoxynol 9 (1%). After their elimination with castor oil using chromatography on insolubilized C18 resin, glycine was added and the pH of the plasma was adjusted to 7.4. Plastic bags were aseptically filled with a mean volume of 200 ml of plasma. The mean levels of coagulation factors were all over 0.7 U/ml and their recovery from initial plasma was nearly the same as total protein except for factor VIII:C. The net loss in factor VIII:C was 16%, when including the dilution of plasma. In vivo and in vitro tests demonstrated that in the final product there were no activated factors. As in fresh frozen plasma, the protein concentrations was over 50

g/l and the potassium level lower than 5 mmol/l. According to these results, virus-inactivated plasma has the same qualities of fresh frozen plasma and could now replace it.

19/7/5 (Item 4 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

9099685 BIOSIS Number: 93084685
SOLVENT-DETERGENT-TREATED PLASMA A VIRUS-INACTIVATED SUBSTITUTE FOR FRESH FROZEN PLASMA
HOROWITZ B; BONOMO R; PRINCE A M; CHIN S N; BROTMAN B; SHULMAN R W
NEW YORK BLOOD CENT., 310 E. STREET, NEW YORK, N.Y. 10021.
BLOOD 79 (3). 1992. 826-831. CODEN: BLOOA
Full Journal Title: Blood
Language: ENGLISH
Fresh frozen plasma (FFP) is prepared in blood banks world-wide as a by-product of red blood cell concentrate preparation. Appropriate clincial use is for coagulation factor disorders where appropriate concentrates are unavailable and when multiple coagulation factor deficits occur such as in surgery. Viral safety depends on donor selection and screening; thus, there continues to be a small but defined risk of viral transmission comparable with that exhibited by whole *blood*. We have prepared a *virus* sterilized FFP (S/D-FFP) by treatment of FFP with 1% tri(n-butyl)phosphate (*TNBP*) and 1% Triton X-100 at 30.degree. C for 4 hours. Added reagents are removed by extraction with soybean oil and chromatography on insolubilized C18 resin. Treatment results in the rapid and complete inactivation of .gtoreq.107.5 infectious doses (ID50) of vesicular stomatitis virus (VSV) and .gtoreq.106.9 ID50 of sinbis virus (used as marker viruses), .gtoreq.106.2 ID50 of human immunodeficiency virus (HIV), .gtoreq.106 chimp infectious doses (CID50) of hepatitis B virus (HBV), and .gtoreq.105 CID50 of hepatitis C virus (HCV). Immunization of rabbits with S/D-FFP and subsequent adsorption of elicited antiboidies with untreated FFP confirmed the absence of neoimmungen formation. Coagulation factor content was comparable with that found in FFP. Based on these laboratory and animal studies, together with the extensive history of the successful use of S/D-treated coagulation factor concentrates, we conclude that replacement of FFP with S/D-FFP, prepared in a manufacturing facility, will result in improved virus safety and product uniformity with no loss of efficacy.

19/7/6 (Item 5 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

8565255 BIOSIS Number: 92030255
THE USE OF TRI-N-BUTYLPHOSPHATE DETERGENT MIXTURES TO INACTIVATE HEPATITIS VIRUSES AND HUMAN IMMUNODEFICIENCY VIRUS IN PLASMA AND PLASMA'S SUBSEQUENT FRACTIONATION
PIET M P J; CHIN S; PRINCE A M; BROTMAN B; CUNDELL A M; HOROWITZ B
BLOOD PROTEIN RES. DEV., NEW YORK BLOOD CENT., 310 EAST 67TH ST., NEW YORK, N.Y. 10021.
TRANSFUSION (ARLINGT) 30 (7). 1990. 591-598. CODEN: TRANA
Language: ENGLISH
The tratment of plasma with organic solvent/detergent mixtures at the time of plasma collection or pooling could reduce the exposure of technical staff to infectious viruses and enhance the viral safety of the final

product. Treatment of plasma for 4 hours with 2-percent tri(n-butyl)phosphate (TNBP) at 37.degree.C, with 1-percent TNBP and 1-percent polyoxyethylensorbitan monooleate (Tween 80) at 30.degree.C, or with 1-percent TNBP and 1-percent polyoxyethylene ethers, (Triton X-45) at 30.degree.C resulted in the rapid and complete inactivation of .gtoreq. 104 tissue culture-infectious doses (TCID50) of vesicular stomatitis and Sindbis viruses, which are used as surrogates. Treatment of *plasma* with *TNBP* and *TNBP* and Tween-80 was shown to inactivate .gtoreq. 104 TCID50 of human immunodeficiency *virus*. *TNBP* treatment of *plasma* contaminated with 106 chimpanzee-infectious doses (CID50) of hepatitis B *virus* and 105 CID50 of non-A,non-B hepatitis *virus* prevented the transmission of hepatitis to chimpanzees. Immediately after treatment of *plasma* with 2-percent *TNBP*, the recovery of factors VIII, IX, and V and antithrombin III was 80, 90, 40, and 100 percent, respectively. Recovery of all factors was .gtoreq. 90 percent after treatment with TNBP and detergent mixtures. Treated plasma was fractionated by standard technique into antihemophilic factor and prothrombin complex concentrates, immune globulin, and albumin. Prior treatment with TNBP or TNBP and detergent did not affect the separations of desired proteins. Therefore, it appears possible to inactivate viruses in plasma before the execution of standard fractionation procedures. If desirable, products prepared from TNBP-treated plasma can be subjected to additional virucidal procedures.

19/7/7 (Item 6 from file: 5)
DIALOG(R)File 5:BIOSIS PREVIEWS(R)

5887185 BIOSIS Number: 84019750
TRI-N-BUTYLPHOSPHATE-DETERGENT TREATMENT OF LICENSED THERAPEUTIC AND EXPERIMENTAL BLOOD DERIVATIVES
EDWARDS C A; PIET M P J; CHIN S; HOROWITZ B
NEW YORK BLOOD CENTER, 310 EAST 67 ST., NEW YORK, NEW YORK 10021.
VOX SANG 52 (1-2). 1987. 53-59. CODEN: VOSAA
Full Journal Title: Vox Sanguinis
Language: ENGLISH
Incubation of an AHF concentrate with 0.3% tri(n-butyl)phosphate (TNBP) and 0.2% sodium cholate was shown to inactivate at least 10,000 infectious doses of lipid-enveloped viruses, including hepatitis B and non-A, non-B viruses and HTLV-III [Prince et al., Lancet i, pp. 706-710, 1986]. The use of *TNBP*/detergent combinations for *virus* sterilization was evaluated further to determine its effect on the structure and function of a wide variety of *blood* proteins. Vesicular stormatitis and Sindbis viruses were used as markers of *virus* inactivation. TNTP/detergent treatment did not significantly alter the function of AHF, factor VII, factor IX, factor X, fibrinogen, factor XIII, fibronectin, anti-HBsAg and anti-HA in normal immune serum globulin, haptoglobulin, tumor necrosis factor, .alpha.-interferon, and both native and chemically polymerized stroma-free hemoglobin. As compared with partially purified derivatives, the extent of *virus* sterilization of plasma and component cryoprecipitate with 0.3% *TNBP* and 0.2% sodium cholate at ambient temperature could be improved by raising the *TNBP* concentration and temperature. *Virus* sterilization by *TNBP*/detergent mixtures appears to be generally applicable to *blood* protein derivatives.

19/7/8 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

7888818 EMBASE No: 90323340
The use of tri(n-butyl)phosphate detergent mixtures to inactivate hepatitis viruses and human immunodeficiency virus in plasma and plasma's subsequent fractionation
Piet M.P.J.; Chin S.; Prince A.M.; Brotman B.; Cundell A.M.; Horowitz B.
Blood Protein Research and Development, The New York Blood Center, 310 East 67th Street, New York, NY 10021 USA
TRANSFUSION (USA) , 1990, 30/7 (591-598) CODEN: TRANA ISSN: 0041-1132
LANGUAGES: English
The treatment of plasma with organic solvent/detergent mixtures at the time of plasma collection or pooling could reduce the exposure of technical staff to infectious viruses and enhance the viral safety of the final product. Treatment of plasma for 4 hours with 2-percent tri(n-butyl)phosphate (TNBP) at 37degreeC, with 1-percent TNBP and 1-percent polyoxyethylensorbitan monooleate (Tween 80) at 30degreeC, or with 1-percent TNBP and 1-percent polyoxythylene ethers, (Triton X-45) at 30degreeC resulted in the rapid and complete inactivation of greater than or equal to104 tissue culture-infectious doses (TCID50) of vesicular stomatitis and Sindbis viruses, which are used as surrogates. Treatment of *plasma* with *TNBP* and *TNBP* and Tween-80 was shown to inactivate greater than or equal to104 TCID50 of human immunodeficiency *virus*. *TNBP* treatment of *plasma* contaminated with 106 chimpanzee-infectious doses (CID50) of hepatitis B *virus* and 105 CID50 of non-A,non-B hepatitis *virus* prevented the transmission of hepatitis to chimpanzees. Immediately after treatment of *plasma* with 2-percent *TNBP*, the recovery of factors VIII, IX, and V and antithrombin III was 80, 90, 40, and 100 percent, respectively. Recovery of all factors was greater than or equal to90 percent after treatment with TNBP and detergent mixtures. Treated plasma was fractionated by standard techniques into antihemophilic factor and prothrombin complex concentrates, immune globulin, and albumin. Prior treatment with TNBP or TNBP and detergent did not affect the separations of desired proteins. Therefore, it appears possible to inactivate viruses in plasma before the execution of standard fractionation procedures. If desirable, products prepared from TNBP-treated plasma can be subjected to additional virucidal procedures.

19/7/9 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

7573136 EMBASE No: 90001739
Efficacy of a *TNBP* -Tween 80 mixture for the inactivation of lipid-enveloped *virus* in *blood* derivatives
EFFICACIA DELLA MISCELA TNBP/TWEEN 80 PER L'INATTIVAZIONE DI VIRUS AD INVOLUCRO LIPIDICO NEGLI EMODERIVATI
Franco E.; Cauletti M.; Iaiani G.; Cini E.; De Santis M.E.
Dipartimento di Sanita Pubblica, II Universita 'Tor Vergata', Via O. Raimondo, 00173 Roma Italy
TRASFUS. SANGUE (Italy) , 1989, 34/5 (241-245) CODEN: TRSAB ISSN: 0041-1787
LANGUAGES: Italian SUMMARY LANGUAGES: English

19/7/10 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

6383627 EMBASE No: 87120286
Tri(n-butyl) phosphate/detergent treatment of licensed therapeutic and experimental blood derivatives
Edwards C.A.; Piet M.P.J.; Chin S.; Horowitz B.
New York Blood Center, New York, NY 10021 USA
VOX SANG. (SWITZERLAND) , 1987, 52/1-2 (53-59) CODEN: VOSAA
LANGUAGES: ENGLISH
Incubation of an AHF concentrate with 0.3% tri(n-butyl)phosphate (TNBP) and 0.2% sodium cholate was shown to inactivate at least *10*,000 infectious doses of lipid-enveloped viruses, including hepatitis B and non-A, non-B viruses and HTLV-III (Prince et al., Lancet i, pp. 706-710, 1986). The use of *TNBP*/detergent combinations for *virus* sterilization was evaluated further to determine its effect on the structure and function of a wide variety of *blood* proteins. Vesicular stomatitis and Sindbis viruses were used as markers of *virus* inactivation. *TNBP*/detergent treatment did not significantly alter the function of AHF, factor VII, factor IX, factor X, fibrinogen, factor XIII, fibronectin, anti-HBsAg and anti-HA in normal immune serum globulin, haptoglobin, tumor necrosis factor, alpha-interferon, and both native and chemically polymerized stroma-free hemoglobin. As compared with partially purified derivatives, the extent of *virus* sterilization of plasma and component cryoprecipitate with 0.3% *TNBP* and 0.2% sodium cholate at ambient temperature could be improved by raising the *TNBP* concentration and temperature. *Virus* sterilization by *TNBP* /detergent mixtures appears to be generally applicable to *blood* protein derivatives.

19/7/13 (Item 1 from file: 159)
DIALOG(R)File 159:Cancerlit(R)

00794888 90385516 MEDL/90385516
THE USE OF TRI(N-BUTYL)PHOSPHATE DETERGENT MIXTURES TO INACTIVATE HEPATITIS VIRUSES AND HUMAN IMMUNODEFICIENCY VIRUS IN PLASMA AND PLASMA'S SUBSEQUENT FRACTIONATION [SEE COMMENTS]
Piet MP; Chin S; Prince AM; Brotman B; Cundell AM; Horowitz B
New York Blood Center, New York.
Transfusion; 30(7):591-8 1990 ISSN 0041-1132 Journal Code: WDN
Contract/Grant No.: 1RO1HL41221
Comment in Transfusion 1991 Nov-Dec;31(9):871
Languages: ENGLISH
Document Type: JOURNAL ARTICLE
The treatment of plasma with organic solvent/detergent mixtures at the time of plasma collection or pooling could reduce the exposure of technical staff to infectious viruses and enhance the viral safety of the final product. Treatment of plasma for 4 hours with 2-percent tri(n-butyl)phosphate (TNBP) at 37 degrees C, with 1-percent TNBP and 1-percent polyoxyethylensorbitan monooleate (Tween 80) at 30 degrees C, or with 1-percent TNBP and 1-percent polyoxyethylene ethers, (Triton X-45) at 30 degrees C resulted in the rapid and complete inactivation of greater than or equal to 10(4) tissue culture-infectious doses (TCID50) of vesicular stomatitis and Sindbis viruses, which are used as surrogates. Treatment of plasma with *TNBP* and *TNBP* and Tween-80 was shown to inactivate greater than or equal to 10(4) TCID50 of human immunodeficiency *virus*. *TNBP* treatment of *plasma* contaminated with 10(6) chimpanzee-infectious doses (CID50) of hepatitis B *virus* and 10(5) CID50

of non-A,non-B hepatitis *virus* prevented the transmission of hepatitis to chimpanzees. Immediately after treatment of *plasma* with 2-percent *TNBP*, the recovery of factors VIII, IX, and V and antithrombin III was 80, 90, 40, and 100 percent, respectively. Recovery of all factors was greater than or equal to 90 percent after treatment with TNBP and detergent mixtures. Treated plasma was fractionated by standard techniques into antihemophilic factor and prothrombin complex concentrates, immune globulin, and albumin. Prior treatment with TNBP or TNBP and detergent did not affect the separations of desired proteins. Therefore, it appears possible to inactivate viruses in plasma before the execution of standard fractionation procedures.(ABSTRACT TRUNCATED AT 250 WORDS)

19/7/14 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09163306 95093306
Possibilities of *virus* inactivation of pooled fresh *plasma* with tri-n-butylphosphate (*TNBP*) detergents (SD procedure)]
Moglichkeiten der Virusinaktivierung von gepooltem Frischplasma mit Tri-n-butylphosphat-(TNBP-)Detergenz (SD-Verfahren).
Gurtler L
Max-von-Pettenkofer-Institut fur Hygiene und Medizinische Mikrobiologie, Ludwig-Maximilians-Universitat Munchen.
Infusionsther Transfusionsmed (SWITZERLAND) Aug 1994, 21 Suppl 1 p77-9 , ISSN 1011-6966 Journal Code: BIW
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English Abstract
Treatment with tri-n-butyl-phosphate and detergent (SD-treatment) leads to efficient inactivation of viruses having a lipid enveloped surface, like hepatitis B virus, hepatitis C virus and human immunodeficiency virus, that are presently the most transfusion relevant viruses in Germany. Other lipid enveloped viruses of the herpes group like cytomegalovirus and Epstein-Barr virus are inactivated as well. Non-enveloped viruses like parvovirus B19 and picornaviruses are not inactivated by SD-treatment. Future inactivation of blood components like plasma and blood products will be a combination of SD- and heat-treatment. Keeping single plasma units in quarantine for 6 months is one of the alternatives in elevating transfusion safety. For transfused blood the safety against infectious agent will continue to depend on the effectiveness of donor selection and the efficacy of testing. (8 Refs.)

19/7/16 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

1022221 82001188734
Inactivation of viruses in labile blood derivaties: I. Disruption of lipid-enveloped viruses by tri(n-butyl)phosphate detergent combinations.
Horowitz, B.; Wiebe, M.E.; Lippin, A.; Stryker, M.H.
New York Blood Cent., 310 E. 67th St., New York, NY 10021, USA
TRANSFUSION; 25(6), pp. 516-522 1985
Language: English Summary Language: English
Document Type: Journal article-original research
Subfile: 22 Virology Abstracts; 01 Microbiology Abstracts A Industrial

RAM Fee History Query
Revenue Accounting and Management

Name/Number: 08532211 Total Records Found: 5
Start Date: Any Date End Date: Any Date

Accounting Date	Sequence Num.	Tran Type	Fee Code	Fee Amount	Mailroom Date	Payment Method
10/13/1995	03006201	1	101	$818.00	09/27/1995	DA 034000
10/13/1995	03006301	1	581	$40.00	09/27/1995	DA 034000
01/16/1997	07010301	1	119	$300.00	12/23/1996	DA 034000
01/16/1997	07010302	1	121	$260.00	12/23/1996	DA 034000
03/14/1997	07002301	1	120	$300.00	02/10/1997	DA 034000

☆ U.S. GOVERNMENT PRINTING OFFICE: 1999-456-878 STAPLE AREA

PATENT NUMBER

APPLICATION SERIAL NUMBER
08/532211

APPLICANT'S NAME (PLEASE PRINT)
Alonso

IF REISSUE, ORIGINAL PATENT NUMBER

ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS
435	236

CROSS REFERENCE(S)				
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)			
424	176.1	177.1	130.1	

INTERNATIONAL CLASSIFICATION	
C 1 2 N	7/04
A 61 K	39/395
A 61 K	39/40
A 61 K	39/42

GROUP ART UNIT: 1646

ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME)

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME)
Yvonne Eyler

PTO 270 (REV. 5-91)

ISSUE CLASSIFICATION SLIP

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

(703) 305-7939

PATENT
MSB-7232

I, Luajuana Riley, do hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail on the date indicated below and is addressed to the Commissioner of Patents and Trademarks, Washington, D. C. 20231.

Luajuana Riley

Luajuana Riley

December 18, 1996

Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: WILLIAM R. ALONSO

Serial No.: 08/532,211

Filed: September 22, 1995

Title: PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

NOTICE OF APPEAL

EXAMINER: Y. EYLER

ART UNIT: 1806

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Applicants hereby appeal the Final Rejection of claims 1-24 mailed September 18, 1996. An Oral Hearing in requested.

Please charge Deposit Account 03-4000 the sum of $560.00 ($300.00 for Notice of Appeal, $260.00 for Oral Hearing request).

Respectfully submitted,

Dated: Dec. 18, 1996

James A. Giblin

James A. Giblin
Attorney for Applicant
Reg. No. 25,772
Bayer Corporation
800 Dwight Way
P.O. Box 1986
Berkeley, CA 94701
(510) 705-7910

2001-1485

Application Serial Number 08/532,211

	DATE	INITIALS
Mail Personnel		
Receive case and PALM in	4-17-01	S.L.
Docket Personnel I		
OB/Heard Classification	7/9/01	mel
Outline case	4/30/01	mel
Reviewers		
Review/assign panel	11/26/01	
Prepare order/remand		
Docket Personnel I		
Enter data in ACTS/PALM		
Prep case (if panel assigned)	RECEIVED	
Docket Personnel I		
Mail remand/order		
Administrators	APR 17 2001	
Assign Hearing Date		
Docket Personnel II	BOARD OF PATENT APPEALS AND INTERFERENCES	
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Legal Technician		
Typed decision	7/29/03	KI
Enter data in ACTS/PALM		
Docket Personnel I		
Send case to _____		

DESIGNATION OF PANEL

Pursuant to (1) the Commissioner's authority to designate the members of the Board of Patent Appeals and Interferences to hear cases before the Board (35 U.S.C. 7(b)), and (2) Commissioner Lehman's memorandum dated May 1, 1994 (delegating to the Chief Administrative Patent Judge the responsibility of designating members to hear cases before the Board), it is ORDERED that the panel of the Board of Patent Appeals and Interferences designated to hear this case shall consist of the following members of the Board:

3/22/3 dem

☒ On Brief / ☐ Heard ☐ Redesignation ☐ Expanded Panel, see addendum.

Place W.Smith Adams

1. Judge Marie Owens
2. Judge ~~Wm. F. Smith~~ Walter Toni Scheiner
3. Judge ~~Mc Kelvey~~ Kimlin

Bruce H Stoner Jr

BRUCE H. STONER, JR.
Chief Administrative Patent Judge

Date of Hearing: _____

BAR CODE LABEL

U.S. PATENT APPLICATION

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT
08/532,211	09/22/95	424	1806

APPLICANT

WILLIAM R. ALONSO, CARY, NC.

CONTINUING DATA********
VERIFIED

_____

FOREIGN/PCT APPLICATIONS********
VERIFIED

_____

FOREIGN FILING LICENSE GRANTED 11/08/95

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS	FILING FEE RECEIVED	ATTORNEY DOCKET NO.
NC	1	24	1	$818.00	MSB-7232

ADDRESS

JAMES A GIBLIN
BAYER CORPORATION
800 DWIGHT WAY
BERKELEY CA 94701

TITLE

PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

This is to certify that annexed hereto is a true copy from the records of the United States Patent and Trademark Office of the application which is identified above.

By authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

Date Certifying Officer

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

Bib Data Sheet

CONFIRMATION NO. 7468

SERIAL NUMBER	FILING DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
08/532,211	09/22/1995 RULE	424	1646	MSB-7232

APPLICANTS

WILLIAM R. ALONSO, CARY, NC;

** CONTINUING DATA **********

** FOREIGN APPLICATIONS **********

IF REQUIRED, FOREIGN FILING LICENSE GRANTED
** 11/08/1995

Foreign Priority claimed	STATE OR	SHEETS	TOTAL	INDEPENDENT
☐ yes ☒ no	COUNTRY	DRAWING	CLAIMS	CLAIMS
35 USC 119 (a-d) conditions met ☐ yes ☒ no ☐ Met after Allowance	NC	1	24	1
Verified and Acknowledged Examiner's Signature Initials				

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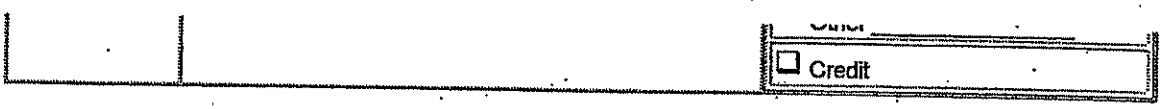
23416
CONNOLLY BOVE LODGE & HUTZ, LLP
1220 N MARKET STREET
P O BOX 2207
WILMINGTON , DE
19899

TITLE
PREPARATION OF VIRALLY INACTIVATED INTRAVENOUSLY INJECTABLE IMMUNE SERUM GLOBULIN

FILING FEE RECEIVED	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other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POSITION		ID NO.	DATE
CLASSIFIER		15	10/22/95
EXAMINER		313	11-3-95
TYPIST		C132	11-8-95
VERIFIER		Dmc	11.8.95
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			
DRAFTING			

INDEX OF CLAIMS

Claim Final	Claim Original	Date 4/1/96	Date 8/15/96	Date 12/17/96	Date 9/8/03
1	(2)	✓	✓	✓	=
2	2	✓			
3	3	✓			
4	4	✓			
5	5	✓			
6	6	✓			
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SYMBOLS

✓ ..... Rejected
= ..... Allowed
- (Through numeral) Canceled
↑ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Claim Final	Claim Original	Date
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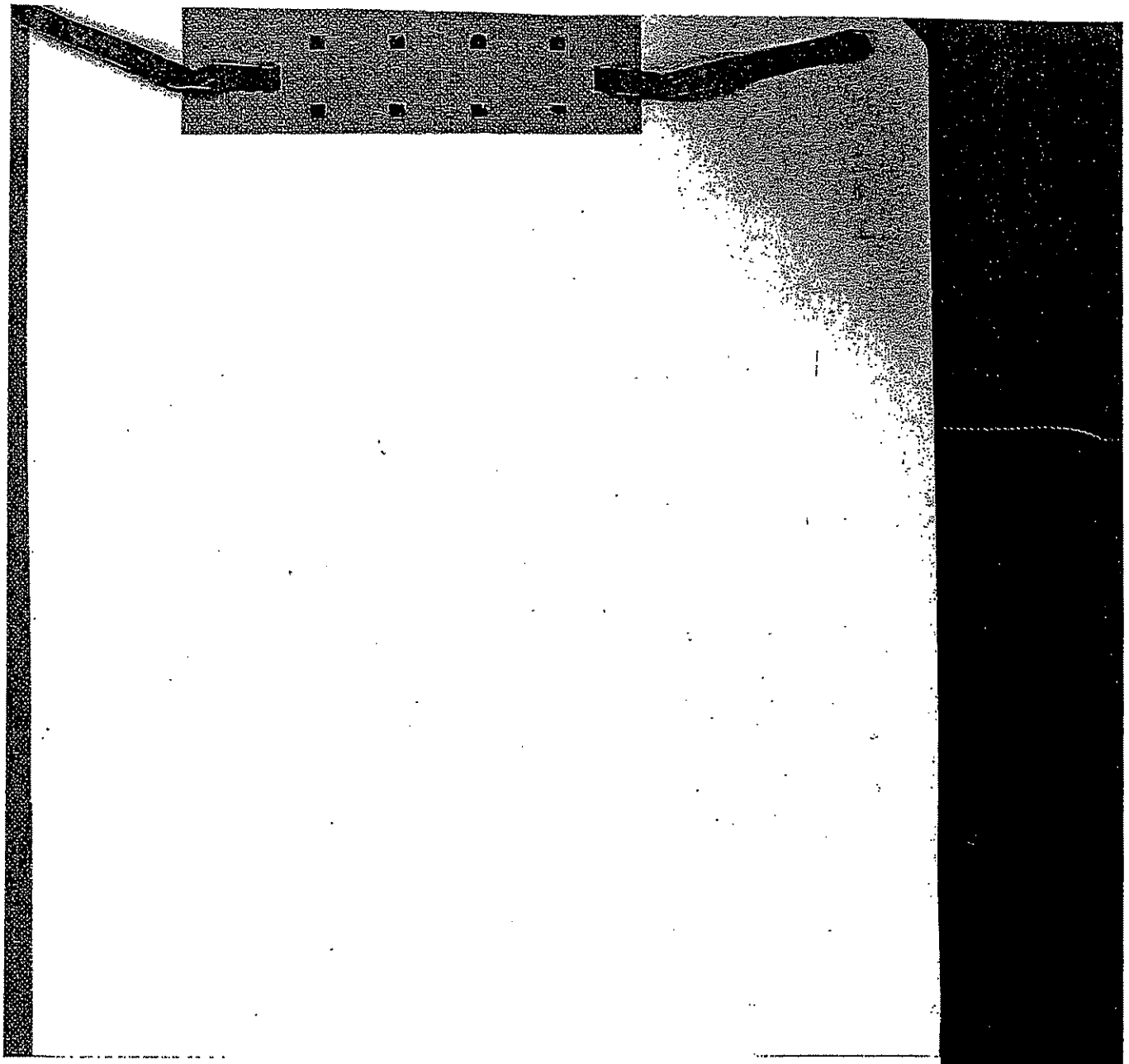

FORM PTO-835 (Rev. 6-82) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE EXAMINATION OUTLINE		DO NOT REMOVE FROM FOLDER	
NUMBER OF CLAIMS 24		NUMBER OF REFERENCES 4	
REJECTIONS 103 112		ACTION SIGNED BY Yvonne Eyler	
CONTINUATION-IN-PART			
CONTINUATION			
CO-PENDING			
BOARD DECISION BY			

[redacted]

SEARCHED

Class	Sub.	Date	Exmr.
530	370.1	1/30/96	YE
	370.5		
	386		
	387.1		
424	176.1		
	177.1		
	130.1		
435	236		
updated		8/15/96	YE
updated		9/8/03	YE

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
435	236	9/8/03	YE
424	176.1		
	177.1		
	130.1		

SEARCH NOTES

	Date	Exmr.
Dialog	1/25/96	YE
APS	1/30/96	YE
updated	8/15/96	YE
Appeal Conference	12/17/97	HBay
updated Search Dialog	9/8/03	YE

(RIGHT OUTSIDE)

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Briefed 1806

APPROVED FOR LICENSE

INITIALS

PATENT APPLICATION

08532211

08/532211

Date Entered or Counted

CONTENTS

Date Received

RECEIVED

NOV 27 1995

1.	Application papers.	9/19/95
2.	RCE & marked	2/19/96
3.	Amdt A	5-14-96 PTO
4.	Rejection final	9-18-96
5.	Amdt B (AE)	11/21/96 Com 11/18/96
6.	Advisory Action	12-23-96
7.	Appeal 01-1495	2-20-97
8.	Appeal Brief	2-20-97
12/30/97 9.	Ex Ans	Dec 31 97
10.	Change Address	2-12-01
11.	Hearing Notice (5/22/03) faxed	03/25/03
12.	Hearing Confirmed	03/25/03
13.	Decision by Board, Reversed	7/24/03
14.	Mot. to Amend	9-11-3
11/23/03 15.	Formal Drawings (1 sheet)	12/22/03
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CERTIFICATE OF SERVICE

I, hereby certify on this 27th day of October, 2006 I electronically filed the foregoing JOINT APPENDIX TO CLAIM CONSTRUCTION BRIEF with the Clerk of Court using CM/ECF which will send notification of such filing to the following:

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